Please amend the subject application as follows:

AMENDMENTS TO THE SPECIFICATION

Please replace the paragraph beginning at page 3, line 1 with the following amended paragraph:

--~~Fig. 1 shows~~ Figs. 1A-1D show that NPM was identified as a substrate of the BRCA1-BARD1 ligase by two different screenings. [*] and [**] represent Myc-BRCA1 (1-772) and HA-BARD1, respectively. In Fig. 1A, a reaction supernatant was analyzed by immunoblotting using an anti-Flag antibody (left panel in Fig. 1A) and the remaining portion was polyubiquitinated and analyzed by nanoscale capillary liquid chromatography-tandem mass spectrometry (LC/MS/MS). In Fig. 1B, anti-flag immunocomplex precipitated from 293T cells expressing one of HA-BARD1 (1-408), wild type Flag-BRCA1 (1-222), or I26A mutant was separated by SDS-PAGE and stained with Sypro Ruby. In Fig. 1C, the association between BRCA1-BARD1 and NPM *in vivo* was confirmed using cells expressed transiently by immunoprecipitation (IP)-Western analysis. Myc-BRCA (1-772), HA-BARD1 and Flag-NPM plasmid were combined and expressed simultaneously in the 293T cells. Total cellular solution (2 panels above Fig. 1C) or immunoprecipitation (IP) was provided to immunoblotting (IB) using anti-HA/Myc, anti-HA antibody with subsequent anti-Myc antibody as re-probes. In Fig. 1D, the 293T solution underwent immunoprecipitation with an antibody to BARD1, and was analyzed by Western blotting.

Please replace the paragraph beginning at page 3, line 4 with the following amended paragraph:

--~~Fig. 2 is a diagram showing~~Figs. 2A-2D are diagrams showing NPM ubiquitination by BRCA1-BARD1. ~~The arrowheads in A indicate the positions of non-ubiquitinated Flag-NPM. The arrowheads in D indicate the positions of ubiquitinated Flag-NPM.~~ [*] represents IgG. In Fig. 2A, Flag-NPM was co-expressed in 293T cells with HA-tagged ubiquitin, Myc-BRCA1 (1-772) and BARD1. Thirty-six hours after co-expression, cells were recovered and boiled in 1% SDS containing buffer, and after being diluted up to 0.1%, Flag-NPM precipitation separated with SDS-PAGE using anti-HA antibody (upper part of Fig. 2A) or anti-Flag antibody (lower part in Fig. 2A) was analyzed by the immunoblotting of NPM. The arrowheads in Fig. 2A indicate the positions of non-ubiquitinated Flag-NPM. In Fig. 2B, *in vivo* ubiquitinated Myc-p53 and Flag-NPM were detected as mentioned above (Fig. 2B, lanes 3 and 6). In Fig. 2C, HA-tagged ubiquitin was co-expressed in 293T cells with Myc-BRCA1 (1-772) and BARD1. Endogenous NPM was immunoprecipitated from 293T cells using 1.5 μg pf anti-NPM antibody, and NPM ubiquitination was analyzed by immunoblotting using anti-HA antibody. In Fig. 2D, recombinant His-Flag-NPM purified by *E.coli* was incubated in the presence of ATP with purified ubiquitin, E1, E2/His-UbcH5c, His-BRCA1 (1-304), and His-BARD1 (14-189). After the reaction product was separated by SDS-PAGE, immunoblotting was performed using anti-Flag antibody. The arrowheads of Fig. 2D indicate the positions of ubiquitinated Flag-NPM.--

Please replace the paragraph beginning at page 3, line 7 with the following amended paragraph:

--~~Fig. 3 is a diagram showing~~<u>Figs. 3A-3C are diagrams showing</u> that NPM ubiquitination by BRCA1-BARD1 is not a signal for the proteolysis by proteasome. In <u>Fig. 3A</u>[[A]], 293T cells were transfected with indicated plasmids: 0.5 μg of Flag-NPM in Lanes 1-4, 0.05 μg of Myc-BRCA1$^{1-772}$ and HA-BARD1 in Lane 2, 0.25 μg of Myc-BRCA1$^{1-772}$ and HA-BARD1 in Lane 3, and 1 μg of Myc-BRCA1$^{1-772}$ and HA-BARD1 in Lane 4. <u>Fig. 3B shows via pulse-chase analysis that BRCA1-BARD1 stabilizes NPM. In Fig. 3C, cells treated with one of the proteasome inhibitors MG132 (20 μM) or LLnL (20 μM) or DMSO solvent for 10 hours. As shown in Fig. 3C, *in vivo* BRCA1-BARD1-mediated ubiquitinated Flag-NPM was detected, but the amount of ubiquitinated Flag-NPM did not decrease.</u>--

Please replace the paragraph beginning at page 3, line 24 with the following amended paragraph:

~~Fig. 6 is a diagram showing~~ <u>Figs. 6A-6D are diagrams showing</u> that CDK2-cyclin A1/E1 and CDK1-cyclin B1 phosphorylates the NH_2-terminal side. * represents IgG, WT represents a wild type, K2/E1 represents CDK2-cyclin E1, K2/A1 represents CDK2-cyclin A1, K1/B1 represents CDK1-cyclin B1, and that HA-BARD1^{-P} represents phosphorylated HA-BARD1. <u>In Fig. 6A, NH_2 terminal (1-320) fragments or COOH terminal (411-777) fragments of Myc-BRCA1$^{1-772}$ and HA-BARD1 were co-expressed with CDK-cyclin or pcDNA3 vector in 293T cells. Fig. 6A shows that when HA-BARD1$^{411-777}$ (COOH terminal fragments 411-777 of</u>

BARD1) was co-expressed with CDK/cyclin, no changes were found. However, when HA-BARD1$^{1-320}$ (NH2 terminal fragments 1-320 of BARD1) was co-expressed with CDK/cyclin, a moderate movement of proteins was observed in the gel. Figs. 6A, 6B and 6D show at least three products were obtained (see arrows) when HA-BARD1$^{1-320}$ was analyzed by immunoblotting. Subsequently, HA-BARD1$^{1-320}$ underwent immunoprecipitation and was analyzed by immunoblotting using anti-HA antibody. HA-BARD1$^{1-320}$ fixed with agarose beads were incubated with alkali phosphatase (AP+) or in a buffer alone (-). Fig. 6C shows that when treated with alkali phosphatase, the aforementioned three products disappeared. These three products were determined to be phosphorylated compounds of BARD1. Fig. 6D shows mapping results of four phosphorylation sites in BARD1 by mutation analysis and identified mutants of BARD1S148A/S251A/S288A/T299A, and also shows almost no changes in molecular weight when using CDK2-cyclin E1 or CDK1-cyclin B1.--